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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,991	11/03/2003	E. Itzhak Lerner	1662/61902	5352

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,991	LERNER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-10 and 18-41* is/are pending in the application.

4a) Of the above claim(s) *19-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7-10, 18, 32-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 7, 2008 have been received and entered into the application.

Action Summary

The rejection of claims 1-18 under 35 U.S.C. 103(a) as being unpatentable over Eichenberger et al. (U.S.Patent No. 4,053,617) in view of Patel et al. (U.S.Patent No. 6,569,463B1) is hereby expressly withdrawn in view of Applicants' amendment.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 7-10, 18 and 32-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Obata Nobuko et al. (JP 09-249562) in view of Patel et al. (U.S.Patent No. 6,569,463B1) of record and further in view of Hoogendoorn et al. (U.S.Patent No. 4,150,113).

Obata Nobuko et al. teach a tizanidine hydrochloride preparation comprising citric acid so that the pH of the preparation is adjusted to $\leq$ 5.5, preferably into the range of 2.2-5.4. Obata Nobuko et al. teach that the preparation can be formulated into tablets, capsules, granules, powder, etc. Obata Nobuko et al. teach that the tizanidine preparation is known as having a muscle relaxant property. (abstract).

Obata Nobuko et al. do not teach buccal or sublingual administration, percentages of bioavailability comparison set forth in claims 7 and 32-34, 37 and 38, the numeric anti-spasmodic amount of tizanidine set forth in claims 35-36, the immediate formulation of tizanidine being compared set forth in claims 8-10 and obtaining saliva with a pH of 2 to 7.

Patel et al. teach that tizanidine composition comprising various excipients can be administered by buccal/sublingual route. (column 28, column 31). Patel et al. teach that the solid buccal or sublingual composition provide a rapidly dissolvable and more solubilized state with improved absorption and/or bioavailability of tizanidine. (column 2, lines 15-40, claims 5-9,23,25, 34,35,37, 49 and 51).

Hoogendoorn et al. teach that as far as pH is concerned, the pH of the saliva is normally about 7.0 to 7.5. Upon the consumption of certain types of foods, particularly, those containing sugar, generation of acid takes place, with lowering the pH down to 5.5 to 4.5. (column 1, lines 45-50).

It would have been obvious to one of ordinary skill in the art to modify the route of administration of Obata Nobuko et al. to sublingual or buccal administration for the treatment of muscle spasms because tizanidine is well known having muscle relaxant

effect and because Patel et al. teach that solid oral tizanidine composition comprising various excipients can be administered via buccal/sublingual route. Further, Patel et al. teach that the buccal or sublingual administration of a composition comprising tizanidine improves the absorption and/or bioavailability of tizanidine. One would have been motivated to make such modification in order to achieve improved absorption and/or bioavailability of tizanidine by rapidly dissolving buccal or sublingual route of administration. There is a reasonable expectation of successfully treating muscle spasm with buccal/sublingual administration of tizanidine formulation taught by Obata Nobuko et al. because Patel et al. teach that buccal/sublingual administration of tizanidine increases bioavailability and improves absorption of tizanidine. The percentages of the drug release and increasing bioavailability of the drug set forth in claims 7 and 32-34, 37 and 38 is obvious result upon the buccal/sublingual administration of the same active agent tizanidine comprising the same acidulant taught by Obata Nobuko et al. would obviously increased bioavailability and absorption of tizanidine. It is noted that the Obata Nobuko et al's tizanidine composition encompasses the same active agent with the same acidulant with the same effective anti-spasmodic amount as required by Applicants' claim 1. With regard to the numeric value of the antispasmodic amount set forth in claims 35 and 36, such is obvious and encompassed by the teaching of Obata Nobuko because Obata Nobuko et al. teach that the tizanidine preparation is known as having a muscle relaxant property. One of ordinary skill in the art would have been motivated to determine its optimum numeric antispasmodic amount in order to provide proper optimum dosages required for the

patients to be treated. With regard to the acidulant (i.e. citric acid) utilized by Obata Nobuko et al. to obtain saliva with a pH of 2 to 7, such is obvious because Hoogendoorn et al. teach that as far as pH is concerned, the pH of the saliva is normally about 7.0 to 7.5. Upon the consumption of certain types of foods, particularly, those containing sugar, generation of acid takes place, with lowering the pH down to 5.5 to 4.5. (column 1, lines 45-50). It is noted that the tizanidine preparation comprising citric acid taught by Obata Nobuko et al. provide pH of $\leq$ 5.5, preferably into the range of 2.2-5.4. Therefore, upon the administration of Obata Nobuko's acidic tizanidine preparation, it would provide saliva with pH less than the normal pH of saliva.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

Response to Arguments

Applicants' arguments filed January 7, 2008 have been fully considered but they are not persuasive. Applicants argue that '463 patent does not disclose or suggest formulations for buccal or sublingual absorption of tizanidine or the 10% increase in bioavailability of AUC_{inf}. This is not found persuasive because the '463 patent teaches that tizanidine composition comprising various excipients can be administered by buccal/sublingual route a solid buccal or sublingual composition and that it absorption and/or bioavailability of tizanidine. Therefore, one would have been motivated to modify

the formulation of tizanidine for sublingual or buccal formulation in order to achieve an improved absorption and/or bioavailability of tizanidine by rapidly dissolving buccal or sublingual route of administration. Further, the % tizanidine increase in bioavailability of AUC_{inf} compared with an immediate release tizanidine enteral dosage form absorbed through the gastro-intestinal track having an equivalent dose of tizanidine is obvious because Obata Nobuko et al. teaches the same tizanidine hydrochloride and citric acid preparation as set forth in Applicants' claims. Therefore, it is reasonably expected that the same tizanidine preparation taught by Obata Nobuko et al, upon the sublingual/buccal administration as modified by Patel would also achieve increase bioavailability compared with the conventional immediate release tizanidine enteral dosage form as well. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire

THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
April 1, 2008